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Strain-Promoted Oxidation of Methylenecyclopropane Derivatives using *N*-Hydroxyphthalimide and Molecular Oxygen in the Dark

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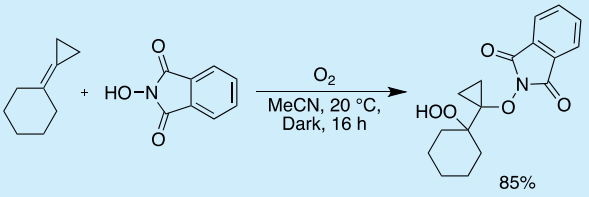
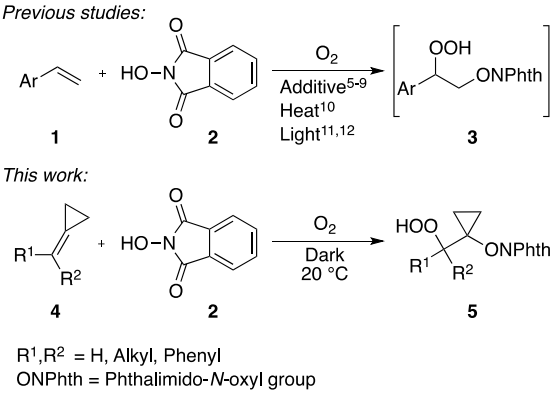
ABSTRACT: The hydroperoxidation of alkylidenecyclopropanes and other strained alkenes using an *N*-hydroxylamine and molecular oxygen occurred in the absence of catalyst, initiator, or light. The oxidation reaction proceeds through a radical pathway that is initiated by autoxidation of the alkene substrate. The hydroperoxides were converted to their corresponding alcohols and ketones under mild conditions.



The oxidation of organic substrates by molecular oxygen provides an inexpensive, environmentally benign method to prepare synthetically useful products.[1−4] Recently, the application of an *N*-hydroxylamine such as *N*-hydroxyphthalimide (NHPI, **2**) in conjunction with molecular oxygen has allowed for the addition of two oxygen atoms across an alkene, affording hydroperoxides as either final products or reactive intermediates (Scheme 1, **1**→**3**).[5−12] NHPI-mediated oxidations proceed through radical pathways that necessitate conversion of NHPI to the phthalimide-*N*-oxyl (PINO) radical through homolytic cleavage of the hydrogen−oxygen bond,[13] a process that requires radical initiators,[9,14,15] transition metals,[5−8,13,16,17] heat,[10,18−20] or light.[11,12,21,22] These transformations generally also require the formation of stabilized alkyl radical intermediates such as benzylic radicals, so they are largely limited to oxidations of styrene derivatives.[23]

Scheme 1. NHPI-Mediated Oxidation of Alkenes



R^1,R^2 = H, Alkyl, Phenyl
ONPhth = Phthalimido-*N*-oxyl group

In this communication, we report the strain-promoted oxidation of aliphatic alkylidenecyclopropanes with molecular oxygen and NHPI (**2**) in the absence of any exogenous activator or catalyst (Scheme 1, **4** → **5**). Other strained alkenes and a different *N*-hydroxylamine also underwent the uncatalyzed transformation. The reaction appears to be initiated by radical intermediates generated upon autoxidation of the alkene, which consequently allows an alkylidenecyclopropane to be employed in catalytic amounts to drive the oxidation of other substrates. These observations extend the use of ring strain to promote reactivity in otherwise inert compounds, a strategy that has been employed in synthetic chemistry,[24−29] chemical biology,[30,31] and materials chemistry.[32−35]

In the course of our studies on the copper-catalyzed oxidations of alkenes,[7] we attempted to extend the scope of the reaction beyond styrenes and enynes. We considered that the reaction could be driven by strain-induced destabilization of the starting alkene, as opposed to stabilization of a radical intermediate. Initial studies treating alkene **4a**, which can be prepared in one step from cyclohexanone,[36] with NHPI open to air justified this hypothesis (Table 1, entry 1). The use of an oxygen atmosphere or blue LED light each resulted in higher yields, but their combined use did not result in a cumulative improvement in yield (Table 1, entries 2−4). A further increase in yield was observed when the reaction mixture was placed in the dark under an oxygen atmosphere, which proved to be the optimal conditions for the reaction (Table 1, entry 6). Unlike under ambient light, in the dark the product yield depended upon the amount of oxygen (Table 1, entry 5). A slight decrease in yield was observed when the concentration was higher (Table 1, entry 8).

The peroxidation reaction was general for a range of methylenecyclopropane derivatives (Scheme 2). The higher yields observed in reactions with bi- and tricyclic tetrasub-

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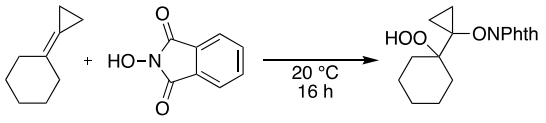
Table 1. Optimization of Reaction Conditions

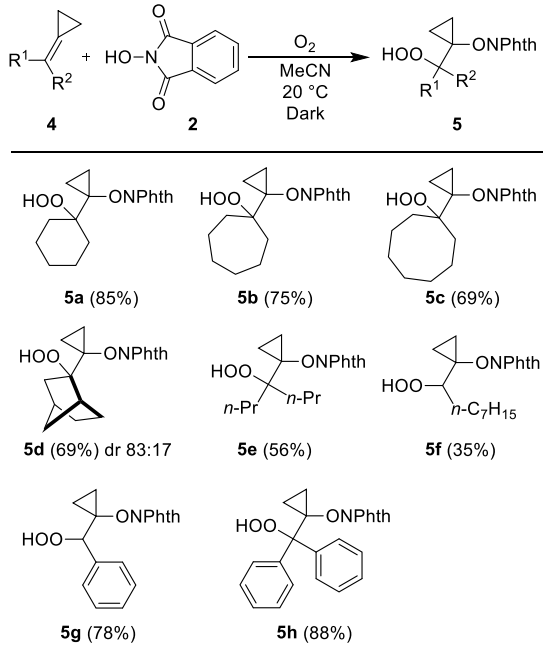


4a **2**, 1.2 equiv **5a**

entry	concn (M)	solvent	light	oxidant	yield[a]
1	0.1	MeCN	ambient	air	65%
2	0.1	MeCN	ambient	O_2	76%
3	0.1	MeCN	blue LED	air	77%
4	0.1	MeCN	blue LED	O_2	77%
5	0.1	MeCN	dark	air	21%
6	***0.1***	***MeCN***	***dark***	***O_2***	***85%***
7	0.05	MeCN	dark	O_2	81%
8	0.5	MeCN	dark	O_2	62%
9	0.1	DCE	dark	O_2	50%
10	0.1	EtOH	dark	O_2	0%
11	0.1	THF	dark	O_2	9%
12	0.1	H_2O	dark	O_2	0%
13	0.1	DMSO	dark	O_2	<1%
14	0.1	acetone	dark	O_2	79%
15	0.1	toluene	dark	O_2	8%

[a]Isolated yields.

Scheme 2. Scope of NHPI-Mediated Oxidation of Alkylidenecyclopropanes[a]

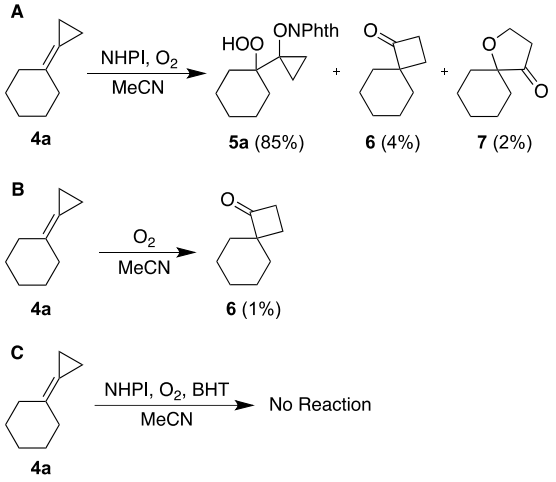


[a]Reaction conditions: **4** (0.50 mmol, 1.0 equiv) and **2** (1.2 equiv) in MeCN (5 mL) for 16 h. Isolated yields.

stituted alkenes **4a**–**4d** compared to that of monocyclic tetrasubstituted alkene **4e** likely result from reduced steric hindrance instead of increased ring strain.[37] The lower yield observed in the case of trisubstituted alkylidenecyclopropane **4f** appears to result from both the lower reactivity of the alkene as well as the instability of the secondary peroxide **5f**. While other substrates were consumed after 16 h, full conversion of **4f** was not observed after 48 h. A longer reaction time did not substantially improve the yield, however.

Minor side products observed following treatment of **4a** with NHPI provided clues as to how the PINO radical could be generated from NHPI in the absence of light, heat, or catalyst.[13] Small amounts of ketones **6** and **7**, among a number of other minor products observed in the unpurified reaction mixture, indicate that molecular oxygen may add directly to the strained carbon–carbon double bond (Scheme 3A). Exposure of **4a** to

Scheme 3. Autoxidation of Alkylidenecyclopropane 4a[a]



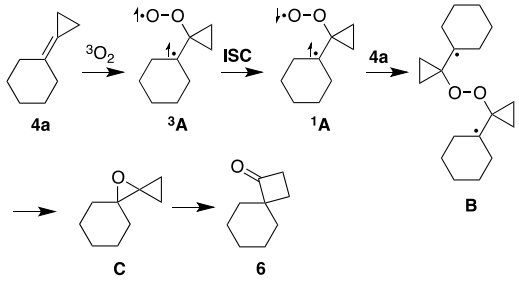
[a]Yields of **6** and **7** were determined by NMR spectroscopy of the unpurified reaction mixture.

oxygen in the absence of NHPI also yielded a trace amount of autoxidation product **6** (Scheme 3B), confirming that oxygen can react directly with the strained alkene.

The autoxidation reactions of alkene **4a** (Scheme 3A,B) appear to proceed through a radical mechanism characteristic of triplet oxygen, as evidenced by the complete inhibition of the reaction in the presence of butylated hydroxytoluene (BHT, Scheme 3C).[38] Although the addition of molecular oxygen to alkenes generally involves the excited singlet state of oxygen,[39] autoxidation reactions of alkenes and alkynes involving triplet oxygen have also been observed.[40−47] Many of these reactions involve geometrically strained compounds,[48−54] including the autoxidations of aryl-substituted alkylidenecyclopropanes.[55,56]

The generation of ketone **6** from the reaction of triplet oxygen with **4a** involves a pathway with several radical intermediates that could react with NHPI to form the PINO radical (Scheme 4). Addition of triplet oxygen to **4a** would initially result in the formation of the triplet diradical ^{3}**A**,[53,54] which could undergo intersystem crossing (ISC) to give the singlet diradical ^{1}**A**.[54,57] Intermediates ^{3}**A** or ^{1}**A** can each react with another molecule of **4a** to form dimer **B** as a triplet or singlet species, respectively.

Scheme 4. Formation of Autoxidation Product 6



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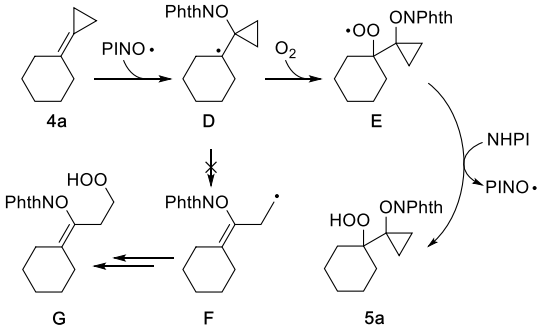
Homolysis of the oxygen−oxygen bond[58] followed by radical recombination would result in epoxide **C**, which can isomerize to cyclobutanone **6** in the presence of trace amounts of acid.[59−61] If ^{3}**A** or ^{1}**A** were sufficiently long-lived to react intermolecularly with **4a**, which the formation of **6** suggests, reaction of these intermediates with NHPI could also occur to form the PINO radical.

Following generation of the PINO radical, the oxidation reaction likely follows a radical addition pathway similar to those previously reported for aryl-substituted alkenes (Scheme 5).[6,8,9,12,62] In this case, however, benzylic or propargylic

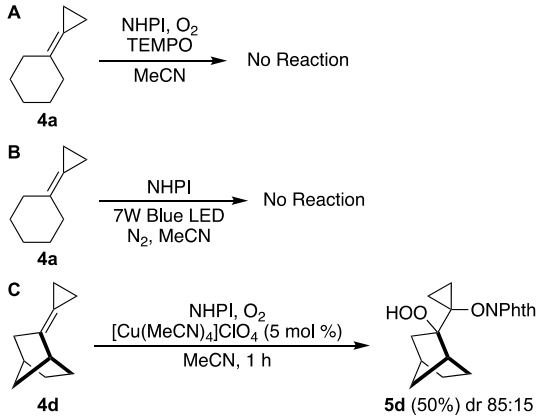
Scheme 5. Proposed Reaction Mechanism



stabilization of the intermediate alkyl radical is not necessary. Instead, the PINO radical adds across the strained carbon−carbon double bond of alkylidenecyclopropane **4a**, generating the more stable alkyl radical **D** instead of the regioisomeric cyclopropyl radical.[63] Addition of molecular oxygen to **D** results in peroxy radical **E**, and subsequent abstraction of hydrogen from a second NHPI molecule yields the *β*-hydroperoxy-*N*-alkoxyamine **5a** and regenerates the PINO radical.

Control experiments support the proposed reaction mechanism (Scheme 6). As observed for experiments conducted in the

Scheme 6. Mechanistic Experiments



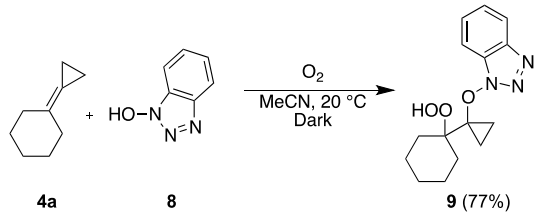
presence of BHT (Scheme 3C), the addition of the radical trap (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) suppressed the reaction (Scheme 6A).[64] No addition products were observed when **4a** was treated with NHPI under a nitrogen atmosphere, indicating that oxygen is necessary for formation of the PINO radical (Scheme 6B).[15,65] Addition of a copper complex known to generate the PINO radical[7] to the reaction mixture resulted in a more rapid conversion of **4d** to the same product as observed under the uncatalyzed conditions (Scheme 6C). The similar diastereoselectivities of the catalyzed and uncatalyzed reactions suggests that they follow a similar pathway.

The involvement of a radical pathway explains why the use of blue light and an oxygen atmosphere, while individually favorable, do not result in a cumulative improvement in yield (Table 1, entries 1−4). Excessive production of the PINO radical, as may be expected with the combined use of light and oxygen, would result in an increase in the second-order decay of radicals through pathways such as dimerization.[66] Accumulation of alkyl and peroxy radicals **D** and **E**, respectively, would also result in increased termination through dimerization and other undesirable side reactions.[67,68] These termination pathways also become more prominent at higher concentrations, resulting in lower yields (Table 1, entry 8).

The fact that products derived from ring-opening of a cyclopropylcarbinyl radical (e.g., **G**) were not observed in any of the peroxidation reactions is not inconsistent with a radical mechanism (Scheme 5).[69] While cyclopropylcarbinyl radical ring-opening proceeds at rates approaching the diffusion limit, this rearrangement can be reversible[70,71] and, in some cases, the ring-closed form is thermodynamically preferred.[72] A preference for the ring-closed form may be expected in this case, as has been observed in similarly substituted cyclopropylcarbinyl radicals, because rearrangement results in a primary alkyl radical.[73]

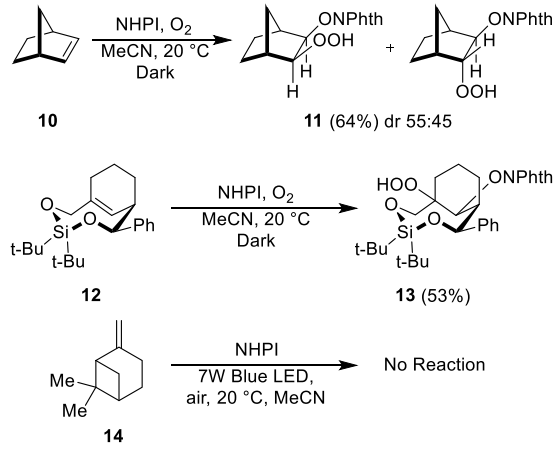
The oxidation reaction was found to be effective with other *N*-hydroxylamines (Scheme 7).[7] Treatment of **4a** with *N*-hydroxybenzotriazole (HOBt, **8**) under the optimized conditions gave peroxide **9** in 77% yield.

Scheme 7. Reaction of Alkylidenecyclopropane 4a with HOBt



Other strained alkenes reacted with NHPI under the same conditions (Scheme 8). Norbornene (**10**) was oxidized to give peroxide **11** as a mixture of diastereomers.[74] While NHPI

Scheme 8. Reaction of Other Strained Alkenes with NHPI



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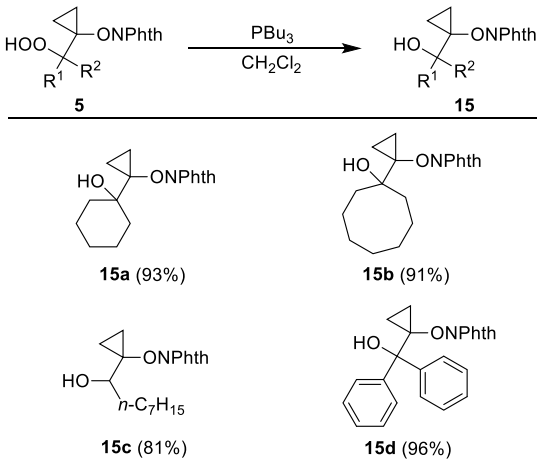
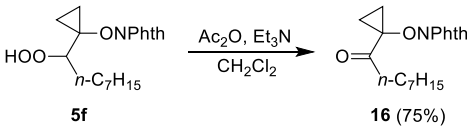
appeared to add selectively to the less hindered *exo* face of the bicyclic system, molecular oxygen added to both the *exo* and *endo* faces due to its high rate of reaction with alkyl radicals.[75] Reaction of *trans*-dioxasilacyclooctene **12** with NHPI proceeded selectively to yield **13**, with the phthalimido-*N*-oxyl group in the pseudoequatorial orientation and oxygen introduced to form the preferred out,out-bicyclo[5.3.1]undecane ring system.[74,76] *β*-Pinene (**14**), which undergoes other strain-promoted reactions,[77,78] is not sufficiently strained to react under the present conditions, even upon irradiation.

The *β*-hydroperoxy-*N*-alkoxyamine products formed in these reactions can be easily functionalized. The hydroperoxide moiety was rapidly reduced to the corresponding hydroxyl group upon treatment with tributylphosphine (Scheme 9). Conversion to the carbonyl group was also possible in the case of a secondary peroxide (Scheme 10).[79]

Scheme 9. Reduction of Peroxides to Alcohols



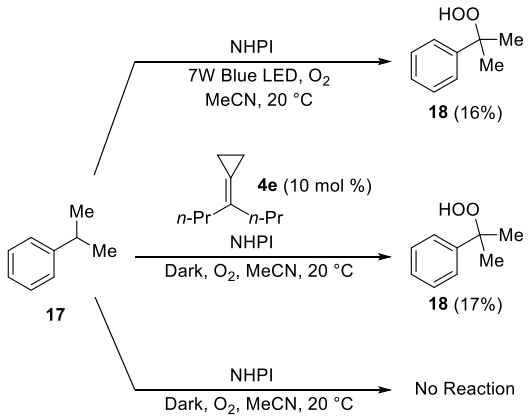
Scheme 10. Elimination of Peroxides to form Ketones



The strain-promoted generation of the PINO radical in the presence of oxygen suggested that other radical reactions could be performed using an alkylidenecyclopropane as an initiator. Treatment of cumene (**17**) with NHPI and a catalytic amount of heptan-4-ylidenecyclopropane **4e** in the dark yielded cumene peroxide (**18**) in an amount comparable to that observed when the same reaction was conducted under blue light without the strained alkene (Scheme 11). No peroxide formation was observed when cumene was treated with NHPI in the absence of **4e** or light. This NHPI-mediated oxidation of a C(sp^3)−H bond in the dark and under mild conditions suggests promise for the use of strained alkenes as radical initiators in other reactions.[80]

In summary, the oxidation of strained alkenes with NHPI and molecular oxygen expands the scope of alkene oxidation reactions. Ring strain not only promotes the addition of the PINO radical to the alkene but also induces formation of this radical. The generation of the PINO radical by the substrate avoids the need for any exogenous activator and suggests the potential use of strained alkenes as cocatalysts in oxidation reactions of other substrates.

Scheme 11. NHPI-Mediated Oxidation of Cumene[a]



[a]Reaction conditions: **17** (1.0 mmol, 1.0 equiv) and NHPI (1.0 equiv), with or without **4e** (10 mol %) in MeCN (10 mL), 22 h. Isolated yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02075.

Experimental procedures, NMR spectra, and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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